Familial partial 14 trisomy

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SUMMARY Four children in the same family have 47,+der(14), t(9;14) (p24;q21). Their mothers are sisters with 46,XX,t(9;14) (p24;q21). Clinical features of the children are similar to those of others reported to have partial 14 trisomy.

Partial 14 trisomy is present in children with similar phenotypic abnormalities and subnormal mental and motor development (Reiss *et al.*, 1972; Short *et al.*, 1972; Muldal *et al.*, 1973; Fryns *et al.*, 1974; Raoul *et al.*, 1975; Turleau *et al.*, 1975; Simpson and Zellweger, 1977). In many instances a balanced translocation is present in the mothers. The I. family (Fig. 1) had 5 daughters with normal intelligence and appearance, 4 of whom had a balanced translocation between chromosomes 9 and 14. Three of these women have borne 7 children: a normal boy, two translocation carriers t(9;14) (p24;q21), and 4 abnormal children manifesting features of partial 14 trisomy, 47+der(14),t(9;14) (p24;q21). There had been one spontaneous abortion.

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Case reports

PATIENT JC (IV.7)

This patient was the first child of healthy parents. He was born in breech presentation at term weighing 2700 g, and had a cleft lip, cleft palate, umbilical hernia, a markedly incurved 5th finger, simple arches on all fingers, an oxycephalic skull narrow towards the front, and distinctive facies. At 16 months, his length, weight, and height were all below the 3rd centile and he was found to have mild spastic quadriplegia. Motor and mental achievements were severely subnormal. He sat at 12 months and did not speak intelligibly until more than 3 years of age. His general IQ was 23 and he was placed in an institution. He suffered occasional generalised tonic-clonic seizures which were controlled with

Fig. 1 Pedigree of family I.

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anticonvulsants. He displayed an ataxic, spastic, broad based, crab-like gait, often causing him to move backwards or sideways.

PATIENT EC (IV.8)

This patient was the younger sister of patient JC. Their mother was found to have untreated diabetes mellitus during this pregnancy, and the patient was born after a gestation of 37 weeks weighing 1970 g, with head circumference 31.5 cm and length 36.5 cm (all less than 3rd centile). The baby had a partial midline cleft palate, a congenitally dislocated right hip associated with bilateral spasticity of hip adductor muscles, capillary haemangiomas of the eyelids, distinctive facies, and mild transient hypoglycaemia. She had single palmar creases, incurved 5th fingers, distal digital dysplasia, thin lips, widely flaring nostrils, shortened philtrum, widened nasal bridge, and microcephaly. Her motor and mental achievements were markedly subnormal and she was placed in an institution.

PATIENT DT (IV.4)

The patient was born at term, weighing 2540 g, after an uneventful pregnancy. No neonatal problems were encountered, but at 16 months of age she was recognised to be retarded in motor, mental, and physical development. She could not walk or talk but could sit with support and pull to a standing posture. Head circumference was 42.6 cm and weight 7.25 kg (below the 3rd centile). X-rays indicated a widespread skeletal dysmorphism with bilateral posterior dislocation of the radial heads, incurved 5th fingers, 11 sets of ribs, and 4 sternal segments. IVP was normal. She was slightly hypotonic and had no evidence of cardiac abnormality.

At 2 years, she first exhibited generalised tonic-clonic seizures which were fairly well controlled on phenytoin and carbamazepine. At 6 years of age she was small (height 86 cm, weight 14.2 kg, head circumference 47 cm), playful, and severely retarded, using a repetitive set of 8 or 10 phrases for all communication. Her skull was oxycephalic, narrow towards the front, and her face dysmorphic with a wide nasal bridge, short philtrum, prominent nostrils, and flaring alae. There was a thin vermilion border on the upper lip and an arched downturned, concave mouth. The palate was high without defect and the ears normally placed with a simple helix. Hypotelorism was present (inner canthal distance 2.3 cm; outer orbital distance 7.4 cm; and interpupillary distance 4.3 cm). She had pectus excavatum, a single palmar crease, distal digital dysplasia and an incurved 5th finger (Fig. 2), 5 arches on the fingertips, and 2 creases on each 5th finger. The electroencephalogram was characterised by bisynchronous 3 to

Fig. 2 Patient DT: Note dysplasia of distal index finger and incurved 5th finger.

3½ c/s spike and wave discharges compatible with generalised motor seizures. Amino acid screening was normal.

PATIENT TC (IV.10)

The patient was born at term to healthy parents. At 30 months of age his weight, height, and head circumference were 9.2 kg, 78.5 cm, and 45.2 cm, respectively, all less than the 3rd centile. He could crawl and use single words, but could not sit, stand, or say 2 words sequentially. Facial dysplasia was characterised by foreshortened philtrum, downturned concave mouth, epicanthal folds, and hypotelorism (outer orbital distance 7 cm; inner canthal distance 2 cm; and interpupillary distance 3 cm). The ears had a simple helix and the skull was oxycephalic, narrow towards the front. There was an incurved 5th finger, distal digital hypoplasia of fingers 1, 2, and 5, minimal soft tissue syndactyly between the 3rd and 4th fingers, and a shallow sacral dimple.

Cytogenetic studies

The karyotypes of the probands and their mothers were determined using quinacrine dihydrochloride (Lin *et al.*, 1971) and acid saline Giemsa (Sumner *et al.*, 1971) stains. The mother of each affected child had a balanced translocation between the long arm

Fig. 3 Karyotype of VC (III.7), 46,XX, t(9p+;14q-). Acid saline Giemsa.

Fig. 4 Karyotype of JC (IV.6), 47,XX, (+14q-). Acid saline Giemsa.

of chromosome 14 and the short arm of chromosome 9 (Fig. 3). This was 46,XX,rcp(9;14) (9pter→9p24::14q21→14pter;14qter→14q21::9p24→9qter). Giemsa 11 (Gagne and Laberge, 1972), done on one of the mothers with the balanced rearrangement, confirmed involvement of chromosome 9 in this translocation. The probands had an extra small acrocentric chromosome (Fig. 4) which, on the basis of banding and maternal karyotypes, was 47,+der (14)rcp(9;14) (p24;q21)mat. The karyotypes of their fathers were normal.

Discussion

The affected children were short and retarded in motor and mental ability. They had microcephaly with oxycephaly, narrow towards the front, and an unusual facial appearance which was dissimilar to their parents and normal sibs (Fig. 5). There was a broad, flat bridge to the nose with prominent alae and a somewhat bulbous tip. The mouth was oval with the lower jaw often hanging slack. The upper lip was slightly arched, downturned, and concave with shortened philtrum. There was an antimongoloid slant and there may have been epicanthi, strabismus, and simple aural helices. The mid-facial and cranial anomalies were subtle without any singular anomaly to aid easy recognition and are best appreciated by comparing pictures of several affected children. Other phenotypic features commonly included an incurved 5th finger and distal digital hypoplasia.

These features are similar to those of other children reported with partial 14 trisomy (Table). They also had multiple anomalies, few of which are lethal. The clinical features of patients with partial 14 trisomy have been summarised recently (Wyandt *et al.*, 1977). At present, there is insufficient data about

persons with pter q21, 22, or 23 to justify confident karyotype/phenotype correlation. However, pictures

Fig. 5 Clockwise from top left: patients JC, DT, EC, and TC to illustrate facies. Note broad, flat nose with bulbous tip, antimongoloid slant to eyes, slack jaw, and foreshortened philtrum with arched upper lip, concave downwards.

Table Features of cases of partial 14 trisomy

	Patient JC	Patient EC	Patient DT	Patient TC	Reiss <i>et al.</i> (1972)	Short <i>et al.</i> (1972)	Muldal <i>et al.</i> (1973)	Fryns <i>et al.</i> (1974)	Raoul <i>et al.</i> (1975)	Turleau <i>et al.</i> (1975)	Simpson and Zellweger (1977)
Mental deficiency	+	+	+	+	+		+	+	+	+	+
Motor subnormality	+	+	+	+	+		+	+	+	+	+
Short stature	+	+	+	+	+		+	+	+	+	+
Downturned mouth	+	+	+	+	+	+	+	+	+	+	+
Cleft palate/lip	+	+	0	0	+	+	0	0	+	+	0
Seizures	+	+	+	+	+	+	+	0	+	+	
Micrognathia	+	+	0	+	+	+	+	0	+	0	
Microcephaly	+	+	+	+	+	+		+	+	0	+
Oxycephaly with anterior narrowing	+	+	+	+					+		
Simian crease	+	+	+	+	0	+			+	0	0
Clinodactyly	+	+	+	+			+		+	0	
Distal digital hypoplasia	+	+	+	+	0		+		+	0	
Carrier mother	+	+	+	+	0	+	0	+	+	+	+

and descriptions indicate that their facial appearance is similar. It is characterised by hypotelorism, short philtrum, and concave mouth. Many have microcephaly and clinodactyly.

In 5 of 7 case reports of partial 14 trisomy, the mother carried a balanced translocation (Short *et al.*, 1972; Fryns *et al.*, 1974; Raoul *et al.*, 1975; Turleau *et al.*, 1975; Simpson and Zellweger, 1977). In one (Muldal *et al.*, 1973), the parents had normal chromosomes, and one patient had a paternal carrier (Reiss *et al.*, 1972). In our family, there was one male carrier (IV.6), who was a child with mild spastic diplegia and mental and developmental retardation. He is at present in the 7th grade and gets along well psychosocially. He has not been tested for IQ. In this family and others in the published reports, there have been no cases of partial 14 monosomy, implying that such a state is nonviable, though partial trisomy for the distal portion of chromosome 14 has been reported (Pfeiffer *et al.*, 1973; Wyandt *et al.*, 1977).

Chromosome 14 is frequently involved in reported translocations. Its long arm fragment has been found translocated onto chromosomes 2, 3, 6, 9, 10, 12, 19, 20, 21, and X (Pfeiffer *et al.*, 1966; Orye and van Nevel, 1968; Alderdice *et al.*, 1971; Reiss *et al.*, 1972; Short *et al.*, 1972; Laurent *et al.*, 1973; Pfeiffer *et al.*, 1973; Fryns *et al.*, 1974; Jacobs *et al.*, 1974; Raoul *et al.*, 1975; Turleau *et al.*, 1975; Simpson and Zellweger, 1977).

The probands were not the product of simple segregation of the mother's chromosomes, but were a tertiary trisomy, the result of 3:1 disjunction during meiosis. Translocated acrocentrics seem predisposed to 3:1 disjunction as do translocated chromosomes with short interstitial segments (Hamerton, 1971; Lindenbaum and Bobrow, 1975). Chromosome 14 is frequently present in reported reciprocal translocations and in subsequent maternal 3:1 disjunction (Lindenbaum and Bobrow, 1975). However, this may reflect an ascertainment bias due to viability of persons with this cytogenetic defect, since studies involving lymphocyte irradiation find no increased involvement of chromosome 14 (Caspersson *et al.*, 1972; San Roman and Bobrow, 1973). Similarly, the reported frequency with which chromosome 9 is involved in translocations (Jacobs *et al.*, 1974) seems influenced by ascertainment bias.

Partial 14 trisomy is associated with a clinically recognisable syndrome of congenital anomalies and mental defects. It has been found in children who are often offspring of balanced translocation carrier mothers. Some families have contained several carriers. Proper genetic counselling requires thorough chromosome evaluation of probands, parents, and other appropriate members of the family.

References

- Alderdice, P. W., Miller, O. J., Miller, D. A., Breg, W. R., Gendel, E., and Zelson, C. (1971). Familial translocation involving chromosomes 6, 14, and 20, identified by quinacrine fluorescence. *Humangenetik*, 13, 205-209.
- Caspersson, T., Haglund, U., Lin-Dell, B., and Zech, H. (1972). Radiation-induced non-random chromosome breakage. *Experimental Cell Research*, 75, 541-543.
- Fryns, J. P., Cassiman, J. J., and Van den Berghe, H. (1974). Tertiary partial 14 trisomy 47,XX,+14q-. *Humangenetik*, 24, 71-77.
- Gagne, R., and Laberge, C. (1972). Specific cytological recognition of the heterochromatic segment of number 9 chromosome in man. *Experimental Cell Research*, 75, 239-242.
- Hamerton, J. L. (1971). *Human Cytogenetics: General Cytogenetics*, Vol. 1, p. 218. Academic Press, New York, and London.
- Jacobs, P. A., Buckton, K. E., Cunningham, C., and Newton, M. (1974). An analysis of the break points of structural rearrangements in man. *Journal of Medical Genetics*, 11, 50-64.
- Laurent, C., Dutrillaux, B., Biemont, M.-Cl., Genoud, J., and Bethenod, M. (1973). Translocation t(14q-;21q+) chez le père. Trisomie 14 et monosomie 21 partielles chez la fille. *Annales de Génétique*, 16, 281-284.
- Lin, C., Uchida, I. A., and Byrnes, E. (1971). A suggestion for the nomenclature of the fluorescent banding patterns in human metaphase chromosomes. *Canadian Journal of Genetics and Cytology*, 13, 361-363.
- Lindenbaum, R. H., and Bobrow, M. (1975). Reciprocal translocations in man. 3:1 meiotic disjunction resulting in 47- or 45- chromosome offspring. *Journal of Medical Genetics*, 12, 29-43.
- Muldal, S., Enoch, B. A., Ahmed, A., and Harris, R. (1973). Partial trisomy 14q- and pseudoxanthoma elasticum. *Clinical Genetics*, 4, 480-489.
- Orye, E., and van Nevel, C. (1968). Familial D/E translocation. *Humangenetik*, 6, 191-199.
- Pfeiffer, R. A., Büttinghaus, K., and Struck, H. (1973). Partial trisomy 14 following a balanced reciprocal translocation t(14q-;21q+). *Humangenetik*, 20, 187-189.
- Pfeiffer, R. A., Keuth, U., Stupperich, E., and Buchner, T. (1966). Klinik und Cytogenetik einer reziproken Translokation zwischen Chromosomen der Gruppen B(4-) und D(13-15). *Beiträge zur Pathologischen Anatomie und zur Allgemeinen Pathologie*, 133, 249-277.
- Raoul, O., Rethoré, M., Dutrillaux, B., Michon, L., and Lejeune, J. (1975). Trisomie 14q partielle. I. Trisomie 14q partielle par translocation maternelle t(10;14) (p15.2;q22). *Annales de Génétique*, 18, 35-39.
- Reiss, J. A., Wyandt, H. E., Magenis, R. E., Lovrien, E. W., and Hecht, F. (1972). Mosaicism with translocation: autoradiographic and fluorescent studies of an inherited reciprocal translocation t(2q+;14q-). *Journal of Medical Genetics*, 9, 280-286.
- San Roman, C., and Bobrow, M. (1973). The sites of radiation induced breakage in human lymphocyte chromosomes, determined by quinacrine fluorescence. *Mutation Research*, 18, 325-331.
- Short, E. M., Solitare, G. B., and Breg, W. R. (1972). A case of partial 14 trisomy 47,XY,(14q-)+ and translocation t(9p+;14q-) in mother and brother. *Journal of Medical Genetics*, 9, 367-373.
- Simpson, J., and Zellweger, H. (1977). Partial trisomy 14q and parental translocation of no. 14 chromosome. *Journal of Medical Genetics*, 14, 124-127.

- Sumner, A. T., Evans, H. J., and Buckland, R. (1971). New techniques for distinguishing between human chromosomes. *Nature*, **232**, 31–32.
- Turleau, C., de Grouchy, J., Bocquentin, F., Roubin, M., and Chavin-Colin, F. (1975). Trisomie 14q partielle. II. Trisomie 14q partielle par translocation maternelle t(12;14) (q24.4;q21). *Annales de Génétique*, **18**, 41–44.
- Wyandt, H., Magenis, R., and Hecht, F. (1977). Abnormal chromosomes 14 and 15 in abortions syndromes and

malignancy. In *New Chromosome Syndromes*, pp. 301–337. Academic Press, New York, San Francisco, and London.

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